lines 7-18; support for new claims 52-57 appear in the specification at page 2, lines 15-20, page 5, lines 26-30, and page 3, lines 7-18; support for new claims 58-63 appear in the specification at page 2, lines 20-24, page 5, lines 26-30, and page 3, lines 7-18; support for new claims 64-69 appear in the specification at page 2, lines 24-29, page 5, lines 26-30, and page 3, lines 7-18; support for new claims 70-75 appear in the specification at page 2, line 32-page 3, line 1, page 5, lines 26-30 and page 3, lines 7-18; support for new claims 76-81 appear in the specification at page 3, lines 1-6, page 5, lines 26-30 and page 3, lines 7-18; support for new claim 82-85 appears in the specification at page 2, lines 29-32, page 5, lines 26-30 and page 3, lines 7-18.

No new matter has been added by this amendment.

112 USC § 112(2)

Claims 17 and 18 are rejected for lack of enablement. The Examiner asserts:

> [The specification] while being enabling for inducing uptake of a bacterial cell by an epithelial cell *in vitro* assays does not reasonably provide enablement for inducing uptake of a bacterial cell by an epithelial cell in a mammal.....
>
> Specification does not disclose a method of inducing uptake of a bacterial cell by an epithelial cell in a mammal comprising expression of the DNA from Salmonella. Furthermore, specification does not teach what that mammal would be.....There are no working examples where a mammal is used for such studies. And also specifciation does not teach how to administer said cell to said mammal. (Page 3, paragraph 2, of the Office Action).

The enablement standard requires that the specification provide a description that, when coupled with the knowledge possessed by a person of ordinary skill in the art, enables that person to make and use the claimed invention. Enablement is not precluded by the necessity for some experimentation, however, any required experimentation must not be undue experimentation.

The Examiner argues above that the specification has three deficiencies. Firstly, the Examiner argues that the specification does not disclose a method of inducing uptake of a bacterial cell by an epithelial cell in a mammal comprising expression of the DNA from Salmonella. To the contrary, the specification on page 25, line 30-page 26, line 4, teaches that

increased expression of SspC and SspD will result in an increase in bacterial-mediated endocytosis (BME). The specification teaches methods of increasing expression of SspC, or SspD, e.g., "introducing multiple copies of the gene(s) into the bacterial cell or cloning the Ssp-encoding DNA under the control of a strong promoter".

Secondly, the Examiner contends that the specification does not teach what the mammal should be and that no working examples where a mammal is used for such studies is presented in the application. The Examiner appears to require an *in vivo* working example. A working example is not required once Applicant has taught those in the art how to perform the claimed method. Applicant has taught that SspC and SspD are critical for invasion of cultured epithelilial cells (page 51, line 27-page 52, line 25). For example a *Salmonella* strain, which was mutated with transposon insertions in genes encoding SspC and SspD was tested for its ability to invade cultured Hep-2 cells. Applicant showed that this strain had more than a "100-fold reduction in invasiveness when compared to wild-type bacteria" (see page 49, lines 25-35). Complementation analysis demonstrated that both SspC and SspD are necessary for *S. typhimurium* invasion of epithelial cells. Methods of manipulating bacterial strains to increase expression of sspC or sspD are taught in the application.

The Examiner's concern that Applicant has not taught which mammal the manipulated bacterial strain can be administered to is undue. Applicant has taught a method of inducing uptake of a bacterial cell by an epithelial cell in a mammal. Applicant has provided an exemplary mammal, a human (on page 6, line 3 of the specification). It is clear from the specification that the manipulated bacterial strains can be administered to any mammal. Applicant sees no reason for specifing a particular mammal. If the Examiner continues to maintain this position, Applicant requests that the Examiner explain his reasoning.

Thirdly, the examiner contends that the specification does not teach how to administer "said cell to said mammal." To the contrary, Applicant teaches that a manipulated bacterial strain can be administered by any of a number of different modes, e.g., by oral or parenteral delivery (see page 8, lines 28-32; and page 24, lines 38-31).

In view of the above remarks, Applicant requests that the Examiner withdraw the rejection.

112 USC § 112(1)

Claims 1 and 3 are rejected as indefinite. Applicant has cancelled claims 1 and 3 rendering the rejection of these claims moot.

Claim 34 is rejected as indefinite because of the recitation of "high stringency conditions". The Examiner contends that "Applicants have not set forth high stringency conditions in the claims or specification". Applicant has cancelled claim 34 rendering the rejection of this claim moot. However, new claims 46, 52, 58, 64, 70, 76 and 82 recite "high stringency conditions" of "50% formamide at 42°C and washing in 0.1 X SSC at 65°C". Applicant would like to point out to the Examiner that the specification does set forth high stringency conditions at page 5, lines 25-35.

35 U.S.C. § 102(e)

WO 95/02098

The Examiner rejects claim 1 as anticipated under 35 U.S.C 102(e) by WO 95/02098. Applicant has cancelled claim 1, rendering the rejection of this claim moot.

Hueck et al.

Claims 1-18 are rejected as anticipated under 35 U.S.C 102(e) by Hueck et al. (*Molecular Microbiology* 18, 579-490, 1995, referred to herein as "Hueck"). Since Hueck is a reference and not a "patent" or an "international application" as required under 102(e), Applicant believes that the Examiner intended to reject the claims under 102(a). Therefore, Applicant will address the rejection as if the claims were rejected under 102(a).

Applicant has cancelled claims 1-16, rendering the rejection of these claims moot. Applicant will address the rejection with respect to claims 17-18 and new claims 46-86.

Hueck does not qualify as prior art under 102(a) because the Hueck reference was published **after** the filing date of the present application. As evidence of this, Applicant has

obtained a date stamped copy of the Hueck reference from Northeastern University, Boston, MA (Exhibit B). The date stamp indicates that the Journal was received by Northeastern University on December 6, 1995. Applicant filed the present application with the U.S. Patent and Trademark Office on November 14, 1995, which is before the Hueck reference was made available to the public. Therefore, the Hueck reference does not qualify as prior art.

Kaniga et al.

Claims 1-4, 7, 10, and 16-18 are rejected under 102(e) as anticipated by Kaniga et al. (Journal of Bacteriology, 177, 3965-3971, 1995; referred to herein as "Kaniga"). For the same reasons as stated above, Applicant believes the Examiner intended to reject these claims under 102(a). Applicant will address the rejection as if the claims were rejected under 102(a).

Applicant has cancelled claims 1-4, 7 and 10, rendering the rejection of these claims moot. Applicant will address the rejection with respect to claims 17-18 and new claims 46-86.

Kaniga discloses the amino acid sequence of SipB and SipC. The earliest date the Kaniga reference was made available to the public was July 8, 1995. As evidence of this date, Applicant submits a letter from Linda Illig, the Director of Journals at the American Society for Microbiology, who states that the issue of the Journal of Bacteriology, which contained the Kaniga reference, was first made available to the public on July 8, 1995 (Exhibit C). As demonstrated in the accompanying Declaration Under 37 C.F.R. § 1.131 of Professor Samuel Miller (Exhibit A), Professor Miller obtained the claimed sequences prior to July 8, 1995. By July 6, 1995, which is before July 8, 1995, Professor Miller had placed in the hands of the publisher a revised and final version of his paper: "Salmonella typhimurium secreted invasion determinants are homologous to Shigella Ipa proteins", *Molecular Microbiology*, 18:479-490 ("the Hueck paper"), which discloses the amino acid sequence of SspA, Ssp, SspC and SspD. See in particular Fig. 4, page 483 of the Hueck paper. In view of the submitted declaration, the rejection of the claims as anticipated by Kaniga should be withdrawn.

Hermant et al.

Claims 1-2, 4, 6, 8, 10 and 16-18 are rejected under 102(e) as anticipated by Hermant et al. (Molecular Microbiology, 17, 781-789, 1995; referred to herein as "Hermant"). For the same

reasons as stated above, Applicant believes the Examiner intended to reject these claims under 102(a). Applicant will address the rejection as if the claims were rejected under 102(a).

Hermant discloses the amino acid sequence of SipA, SipB, SipC, SipD and SipE. The Hermant reference was made available to the public on October 3, 1995. As evidence of this, Applicant has obtained a date stamped copy of the Hermant reference from Massachusetts Institute of Technology (MIT), Cambridge, MA (Exhibit D). The date stamp indicates that the Journal was received by MIT on October 3, 1995. As demonstrated in the accompanying Declaration Under 37 C.F.R. § 1.131 of Professor Samuel Miller (Exhibit A), Professor Miller obtained the claimed sequences prior to October 3, 1995. By July 6, 1995, which is before October 3, 1995, Samuel Miller had placed in the hands of the publisher a revised and final version of his paper: "Salmonella typhimurium secreted invasion determinants are homologous to Shigella Ipa proteins", *Molecular Microbiology*, 18:479-490, ("the Hueck paper"), which discloses SspA, SspB, SspC and SspD. See in particular Fig. 4, page 483 of the Hueck paper. In view of the submitted declaration, the pending claims are not anticipated by the Hermant reference.

In view of the above remarks, the pending claims are not anticipated by Kaniga, Hermant or WO 95/02098. Applicant requests withdrawal of the anticipation rejection.

Conclusion

In view of the foregoing amendment, remarks, and supporting document, Applicant requests the examiner to reconsider this application. Applicant submits that the application is in condition for allowance. Such action is requested. If the Examiner finds that a telephone conference would advance the prosecution of this application, he is invited to telephone the undersigned at the number provided below.

Filed herewith is a check in payment of the excess claims fees required by the above amendments and Petition for Automatic Extension with the required fee.

Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 14 APRIL 2000

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